WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 5, 127-142. Research Article ISSN 2277– 7105

RISK FACTORS FOR SURGICAL INTERVENTION OF EARLY MEDICAL ABORTION

Abire Abdalmahdi Hussein* and Israa Abdulmunem Mohammed

Ministry of Health - Baghdad Medical Office - Al-Karkh, Al Karama Educational Hospital, Baghdad, Iraq.

Article Received on
03 Feb. 2019,

Revised on 24 Feb. 2019,
Accepted on 18 March 2019

DOI: 10.20959/wjpr20195-14550

***Corresponding Author**
Abire Abdalmahdi Hussein
Ministry of Health - Baghdad Medical office - Al-Karkh, Al Karama Educational Hospital, Baghdad, Iraq.

ABSTRACT

Based on efficacy and adverse effect profile, evidence-based protocols for medical abortion are superior to the FDA-approved regimen. Vaginal, buccal, and sublingual routes of misoprostol administration increase efficacy, decrease continuing pregnancy rates and increase the gestational age range for use as compared with the FDA-approved regimen. Regimens that use low doses of mifepristone (200 mg) have similar efficacy and lower costs compared with to those that use mifepristone at 600 mg Women can safely and effectively self-administer misoprostol at home as part of a medical abortion regimen. Medical abortion also can be provided safely and effectively by nonphysician clinicians. Follow-up after receiving mifepristone and misoprostol for medical abortion is important, although an in-clinic evaluation is not always necessary. Misoprostol-only medical abortion regimens are significantly less effective than those that use a combination of mifepristone and misoprostol.

KEYWORDS: Surgical intervention, early medical abortion.

INTRODUCTION

Over the past three decades, medical methods of abortion have been developed throughout the world and are now a standard method of providing abortion care in the United States. Medical abortion, which involves the use of medications rather than a surgical procedure to induce an abortion, is an option for women who wish to terminate a first-trimester pregnancy. Although the method is most commonly used up to 63 days of gestation (calculated from the first day of the last menstrual period), the treatment also is effective after 63 days of

gestation. The Centers for Disease Control and Prevention estimates that 64% of abortions are performed before 63 days of gestation.[1]

Medical abortions currently comprise 16.5% of all abortions in the United States and 25.2% of all abortions at or before 9 weeks of gestation.[1] Mifepristone, combined with misoprostol, is the most commonly used medical abortion regimen in the United States and Western Europe; however, in parts of the world, mifepristone remains unavailable. This document presents evidence of the effectiveness, benefits, and risks of first-trimester medical abortion and provides a framework for counseling women who are considering medical abortion.[2]

BACKGROUND

Medications currently used for medical abortion

Mifepristone

Mifepristone, a derivative of norethindrone, binds to the progesterone receptor with an affinity greater than progesterone itself but does not activate the receptor, thereby acting as an antiprogestin.[3] Its known actions on a uterus in pregnant women include decidual necrosis, cervical softening, and increased uterine contractility and prostaglandin sensitivity.[4] Human studies have suggested that uterine contractility does not increase until 24–36 h after mifepristone administration.[5]

At this point, the sensitivity of the myometrium to the stimulatory effects of exogenous prostaglandins increases fivefold.[6] However, more recent studies have shown high efficacy when vaginal misoprostol is administered less than 15 min after mifepristone.[7] The effectiveness of such a regimen cannot be attributed to the actions of the misoprostol because misoprostol alone has much lower efficacy than mifepristone. Accordingly, these studies suggest that some or all of these actions occur sooner than previously believed or that the effects of mifepristone that are important and necessary for its abortifacient activity remain incompletely understood.

As a progesterone receptor antagonist, mifepristone also has several other potential medical applications, including emergency contraception; cervical ripening and labor induction; and treatment of symptomatic uterine leiomyomas, endometriosis, Cushing syndrome, breast cancer, early pregnancy loss, and glaucoma.[8]

Misoprostol

Misoprostol is an inexpensive prostaglandin E1 analog in a tablet form that is stable at room temperature. It is approved by the US Food and Drug Administration (FDA) for oral administration to prevent gastric ulcers in individuals who take anti-inflammatory drugs on a long-term basis, and it is included in the FDA-approved labeling of mifepristone for use in abortion. It is used off-label in other regimens for abortion, labor induction, treatment of early pregnancy loss, prevention and treatment of postpartum hemorrhage, and cervical priming before uterine procedures, such as hysteroscopy.[9] Pharmacokinetic evaluations of misoprostol absorption, when administered by various routes, have been performed.[10] Routes that result in a longer duration of action (i.e., buccal and vaginal) also appear to result in greater efficacy compared with oral administration. Similarly, those routes with rapid and significant absorption (i.e., sublingual) also have high efficacy, but the greater maximum concentration results in more adverse effects. Misoprostol-only medical abortion regimens are significantly less effective than those that use a combination of mifepristone and misoprostol.[11]

Other agents

Methotrexate in combination with misoprostol was adopted in the United States and Canada as an alternative to mifepristone regimens before mifepristone was available.[12] However, methotrexate rarely is used anymore in the United States for medical abortion because of the greater availability and efficacy of mifepristone regimens.

Methotrexate blocks dihydrofolate reductase, an enzyme involved in producing thymidine during DNA synthesis. Methotrexate exerts its action primarily on the cytotrophoblast rather than the developing embryo, which inhibits syncytialization of the cytotrophoblast.[13]

Thus, methotrexate stops the process of implantation rather than weakening the implantation site directly. In contrast, the antiprogestin mifepristone has no direct effect on the trophoblast. Tamoxifen has been used in some studies of early abortion in combination with misoprostol. However, randomized trials have demonstrated no benefit of using tamoxifen–misoprostol over methotrexate–misoprostol or misoprostol alone regimens.[14] Two small studies from China suggest that multiple daily administrations of letrozole followed by misoprostol, 800 mcg vaginally, maybe another effective option for medical abortion, but more research is needed regarding this regimen.[15]

Mifepristone regimens Regimen approved by the US Food and Drug Administration The FDA-approved regimen, as detailed in the mifepristone package labeling, is based on the original regimen registered in France 25 years ago. This regimen includes mifepristone, 600 mg orally, followed approximately 48 h later by a prostaglandin analog, usually misoprostol 400 mcg orally.[16]

The FDA-approved regimen includes this treatment with a follow-up visit approximately 14 days after mifepristone administration[17]. If clinical history indicates that the woman had a confirmed abortion, a pelvic examination is performed to confirm uterine involution. If clinical history and physical examination do not confirm expulsion, ultrasonography is performed. Suction aspiration at the follow-up evaluation is not specified as necessary unless the pregnancy is ongoing.[18]

The efficacy of the FDA-approved regimen is approximately 92% in women with gestations up to 49 days.[19] Complete abortion rates are higher with earlier gestations; approximately 96–98% in gestations of up to 42 days, 91– 95% in gestations from 43 days to 49 days, and less than 85% in gestations beyond 49 days.[20] When abortion does not occur within 3–4 h after oral misoprostol administration, use of an additional dose does not improve efficacy.[21]

Evidence-based regimens Additional "evidence-based" regimens have been developed to improve medical abortion in terms of expense, safety, speed, and adverse effects. Regimens that use low doses of mifepristone (200 mg) have similar efficacy and lower costs compared with those that use mifepristone at 600 mg.[22]

Based on efficacy and the adverse effect profile, evidence-based protocols for medical abortion are superior to the FDA-approved regimen. Vaginal, buccal and sublingual routes of misoprostol administration increase efficacy, decrease continuing pregnancy rates and increase the gestational age range for use as compared with the FDA-approved regimen.[23] By changing the route of misoprostol administration, the timing between mifepristone and misoprostol dosing can be varied to allow women more flexibility to accommodate personal situations, such as work and childcare. Regimens that use vaginal misoprostol can be provided simultaneously with mifepristone to terminate gestations of up to 63 days.[24]

A6–the 8-h interval between mifepristone administration and vaginal misoprostol administration is as effective as a 24-h interval and results in significantly fewer adverse

effects.[25] Buccal and sublingual misoprostol can be administered as early as 24 h after mifepristone administration. Women can safely and effectively self-administer misoprostol at home as part of a medical abortion regimen.[26]

Medical abortion vs. surgical abortion Counseling must first emphasize early pregnancy options to ensure that a woman is certain about her decision to have an abortion. If she is uncertain, then the decision about abortion technique must be delayed until she has reached a firm decision, even if the delay means that she will be unable to choose a medical option. Only when a woman has considered her options and decided to have an abortion does the discussion about the different methods become an issue. Most women who seek an early abortion will be eligible for medical and surgical methods. The general advantages and disadvantages of each approach should be explained early in the counseling process (Box 1).[36–38] Even for women who think they are unsure about the method, most will have some preference after counseling.[27]

Studies that have compared abortion method preferences have included groups of patients who choose their method and those who are randomized to their method. The applicability of these studies to current US medical abortion practice is limited given that no studies included the mifepristone-misoprostol regimen, and in two studies, surgical abortion was performed only under general anesthesia. Generally, women are satisfied with the method they choose but, when randomized, prefer surgical abortion to medical abortion.[28]

Most women choose medical abortion because of a desire to avoid surgery, a perception that medical abortion is safer than surgical abortion, and a belief that medical abortion is more natural and private than a surgical procedure.[29] Compared with surgical abortion, medical abortion takes longer to complete, requires more active patient participation, and is associated with higher reported rates of bleeding and cramping. With medical abortion, the expulsion of the products of conception most likely will occur at home, but a few women will still require surgical evacuation to complete the abortion. An early surgical abortion takes place most commonly in one visit and involves less waiting and less doubt about when an abortion occurs compared with medical abortion. In addition, women who undergo a surgical abortion will not see any products of conception or blood clots during the procedure.[30]

Bleeding and cramping will be experienced by most women undergoing a medical abortion and are necessary for the process to occur. Adverse effects commonly associated with

mifepristone use include nausea, vomiting, diarrhea, headache, dizziness, and thermoregulatory effects.[31] The incidence of each adverse effect is based on the regimen used (especially the prostaglandin analog), the dose and route of administration of the prostaglandin analog and the gestational age. Gastrointestinal adverse effects are less common when misoprostol is administered vaginally as compared with regimens that use oral, buccal, or sublingual misoprostol.[32] Buccal and sublingual administration cause similar adverse effects, with the sublingual route associated with a higher rate of chills.[33] Counseling should emphasize that the woman is likely to have bleeding that is much heavier than menses (and potentially with severe cramping) and is best described to patients as compared with a miscarriage. The woman should understand how much bleeding is considered too much. An easy reference for the patient to use is the soaking of two maxi pads per hour for 2 consecutive hours.[34]

Patients should be advised to call their health care providers if they experience this level of bleeding. The need for emergency care is based on how the patient is feeling, her baseline hemoglobin (Hb) or hematocrit level, whether the bleeding seems to be slowing, and her distance from an emergency facility. Overall, large series demonstrate that less than 1% of women will need emergency curettage because of excessive bleeding.[35] Moreover, the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days[36]; this risk will vary based on the regimen used. Pain management is an important consideration.

The woman should be sent home with appropriate instructions for analgesia with over-the-counter medications and can be provided with prescriptions for oral narcotics to use when needed. Nonsteroidal anti-inflammatory drugs, such as ibuprofen, are not contraindicated in women who undergo a medical abortion and are appropriate first-line agents for pain management. One randomized trial found that ibuprofen taken when needed was more effective than acetaminophen to reduce pain associated with medical abortion.[37]

Nonsteroidal anti-inflammatory drugs inhibit the synthesis of new prostaglandins, but they do not block the action of prostaglandin receptors and should not inhibit the action of a prostaglandin used for medical abortion. In a retrospective analysis of nonsteroidal anti-inflammatory drugs and complete abortion, in 416 women who received misoprostol after methotrexate for the medical abortion of gestations up to 56 days, the use of ibuprofen did

not interfere with the action of misoprostol to induce uterine contractions and expulsion of the products of conception.[38] One randomized trial found that multiple doses of ibuprofen given prophylactically at the time of misoprostol administration did not significantly reduce pain associated with medical abortion compared with ibuprofen taken when needed.[39]

Need for surgical evacuation

The overall rate of surgical evacuation with medical abortion varies greatly based on the regimen used, the gestational age of the pregnancy, and many other factors. In most studies of medical abortion of gestations up to 63 days with mifepristone 200 mg followed by misoprostol, less than 5% of patients undergo surgical evacuation.[40] To determine whether a surgical evacuation is needed, it is important to distinguish incomplete abortion from the normal course of a medical abortion. When an ultrasound examination is performed at the follow-up visit, the sole purpose is to determine whether the gestational sac is present.

After surgical or spontaneous expulsion, the uterus will normally contain sonographically hyperechoic tissue that consists of blood, blood clots, and decidua. Rarely does this finding in women who have undergone medical abortion indicate a need for intervention. In the absence of excessive bleeding, health care providers can monitor such patients based on symptoms. Guidelines for intervention vary for women who have a persistent gestational sac on ultrasonography without evidence of embryonic cardiac activity or continuing development. Patients with a persistent gestational sac 1 week after treatment can safely receive another dose of misoprostol or continue with expectant management.[41] Studies indicate that even with a retained sac 2 weeks after mifepristone, intervention is unnecessary and that expulsion will typically occur in the ensuing weeks.[42] Women who prefer not to wait longer may choose to have a surgical evacuation at any time. Most commonly, women who are awaiting delayed expulsion will no longer feel pregnant or have medication-induced symptoms; patients will be waiting for the onset of bleeding or cramping similar to anticipating the start of menses.[43] Health care providers must differentiate these women from those who have incomplete expulsion of the pregnancy tissue with symptoms, such as prolonged and irregular bleeding episodes. Continuing pregnancies are typically reported in less than 1% of women who begin medical abortion at or before 63 days of gestation with evidence-based regimens.[44] Ongoing pregnancy may be treated with uterine aspiration or a repeat dose of vaginal misoprostol. In an analysis of data from two randomized trials with 14 cases of ongoing pregnancy with gestational cardiac activity, treatment with a repeat dose of

misoprostol, 800 mcg administered vaginally, resulted in expulsion of the products of conception in five cases (36%); in an additional four cases (29%), gestational cardiac activity was no longer present at the next follow-up visit.[45]

If gestational cardiac activity persists at follow-up after the second dose of misoprostol, uterine aspiration should be performed. Repeat doses of buccal misoprostol to treat ongoing pregnancy have not been studied. Women who undergo medical abortion may need to access emergency surgical intervention, and it is medically appropriate to provide a referral to another health care provider. However, state or local laws may have additional requirements. In women who receive mifepristone and vaginal misoprostol, emergency curettage within the first 24 h of treatment is rare, occurring in 0.2% of patients.[46]

Clinicians who wish to provide medical abortion services either should be trained in surgical abortion or should be able to refer to a clinician trained in surgical abortion.

In addition to physicians, advanced practice clinicians, such as nurse–midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion.[47] In a randomized controlled trial in Nepal, women randomized to receive a medical abortion under the care of a staff nurse had a statistically equivalent risk of complete abortion compared with those under the care of a physician, and no serious adverse events were reported.[48]

This evidence indicates that medical abortion also can be provided safely and effectively by nonphysician clinicians, and in some states, advanced practice clinicians are allowed to provide medical abortion. However, many states require that a physician perform an abortion and prohibit the provision of medical abortion by nonphysician clinicians. Telemedicine, which involves the use of video and information technology to provide a medical service at a distance, has been used to extend the reach of physicians to provide medical abortion. In one model, patients seen at a clinic without an on-site physician have a video consultation with a physician located elsewhere.[49]

The physician is able to review electronically the patient's medical history, and ultrasonography, if requested, can be performed by a trained technician at the remote clinic. If the patient is eligible for medical abortion, the physician remotely opens a telepharmacy drawer containing the mifepristone and misoprostol and instructs the patient how to use it.

This model was evaluated in a nonrandomized study and found to be equally effective when compared with an in-person visit with a physician; adverse events, including ongoing pregnancy, occurred in 1.3% of patients and were not statistically different between the two groups.[50] Women who chose telemedicine medical abortion were significantly more likely to say they would recommend the service to a friend compared with women who had an in-person visit with a physician.[51]

In an analysis of this clinic system's service-delivery statistics, after telemedicine was introduced, a significant reduction in second-trimester abortion was reported, and women in remote parts of the state were more likely to obtain an abortion than before.[52]

Medical abortion can be provided safely and effectively via telemedicine with a high level of patient satisfaction; moreover, the model appears to improve access to early abortion in areas that lack a physician health care provider. Despite the medical evidence, several states have passed legislation that bans the use of telemedicine to provide abortion.[53]

Recommended timing of contraception provision after medical abortion

Almost all contraceptive methods can be provided immediately after the uncomplicated first-trimester medical abortion, and all are considered Category 1 for provision after first-trimester abortion according to the U.S. Medical Eligibility Criteria (meaning there is no restriction for use).[54] Oral contraceptives, patch, ring, depot medroxyprogesterone acetate, and subdermal implants all may be started on the day of misoprostol administration.[55] However, this requires an additional visit to the clinic to start depot medroxyprogesterone acetate and implants, and research is exploring whether these methods can be administered on the day of mifepristone without reducing the efficacy of medical abortion. The optimal timing of IUD insertion has been evaluated in two randomized studies. One study randomized woman to insertion of a copper IUD 1 week after mifepristone vs. 4−6 weeks later.[56] Significantly more women in the early insertion group received an IUD (97% vs. 76%, pb.001). Another study randomized woman to insertion of either a copper or levonorgestrel-containing IUD 5−9 days after mifepristone vs. 3−4 weeks later.[57]

Fewer women in the delayed group attended the follow-up visit to insert the IUD (1.5% vs. 11%, p=.03). In both studies, no significant difference was found in expulsion rates by the group; however, the delayed-insertion groups had expulsion rates of 7−11%, which is higher than the expulsion rate noted with immediate IUD insertion after a surgical abortion.[58] The

risk of expulsion of an IUD needs to be weighed against the risk that the patient will not return for a delayed insertion. Sterilization may be performed once abortion is confirmed.

RESULTS

Compared to nulliparous women, a history of only vaginal deliveries with spontaneous delivery of placenta implied an OR of 1.1 (95% CI 1.0–1.2), women with a history of at least one cesarean section an OR of 1.5 (95% CI 1.3–1.6), and women having experienced a manual removal of placenta after a vaginal birth an OR of 2.0 (95% CI 1.7–2.4). Previous medically induced abortion decreased the risk of surgical intervention, OR 0.84 (95% CI 0.78–0.91), whereas previous early (before 56 days of gestation) surgically induced abortion implied a 53% (95% CI 1.4–1.7) increased risk of surgical intervention. Previous surgical abortion after 55 days of gestation increased the risk by 17% (95% CI 1.1–1.3). The AUC of the model including all quantified risk factors was 63% (95% CI 62-64%).

Gestational age, maternal age, previous deliveries, and history of medically and surgically induced abortions all had a significant influence on the risk of surgical intervention of early medical abortion. However, the inclusion of all quantified risk factors still left most interventions unpredictable.

DISCUSSION

Because teratogenicity of medical abortifacients becomes an important issue if the pregnancy continues, patients must be counseled before medical abortion treatment of the need for a surgical abortion in the event of continuing pregnancy.

Before a medical abortion is performed, gestational age should be confirmed by clinical evaluation or ultrasound examination.

Nonsteroidal anti-inflammatory drugs, such as ibuprofen, are not contraindicated in women who undergo a medical abortion and are appropriate first-line agents for pain management.

Buccal administration of misoprostol may result in a lower risk of serious infection compared with vaginal administration. Medical abortion can be provided safely and effectively via telemedicine with a high level of patient satisfaction; moreover, the model appears to improve access to early abortion in areas that lack a physician health care provider.

The following recommendations are based primarily on consensus and expert opinion (Level C): Women who undergo medical abortion may need to access emergency surgical intervention, and it is medically appropriate to provide a referral to another health care provider. However, state or local laws may have additional requirements.

Clinicians who wish to provide medical abortion services either should be trained in surgical abortion or should be able to refer to a clinician trained in surgical abortion.

No strong data exist to support the universal use of prophylactic antibiotics for medical abortion.

Rh testing is standard of care in the United States, and RhD immunoglobulin should be administered if indicated.

REFERENCES

1. Pazol K, Creanga AA, Zane SB, Burley KD, Jamieson DJ. Abortion surveillance–United States, 2009. Centers for Disease Control and Prevention (CDC). MMWR Surveill Summ, 2012; 61(SS-8): 1-44. (Level II-3).
2. Gravanis A, Schaison G, George M, de Brux J, Satyaswaroop PG, Baulieu EE, et al. Endometrial and pituitary responses to the steroidal antiprogestin RU 486 in postmenopausal women. J Clin Endocrinol Metab, 1985; 60: 156-63. (Level III).
3. Swahn ML, Bygdeman M. The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin. Br J Obstet Gynaecol, 1988; 95: 126-34. (Level II-3).
4. Johannisson E, Oberholzer M, Swahn ML, Bygdeman M. Vascular changes in the human endometrium following the administration of the progesterone antagonist RU 486. Contraception, 1989; 39: 103-17. (Level III).
5. Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: a randomized controlled trial. Medical Abortion at the Same Time (MAST) Study Trial Group. Obstet Gynecol, 2007; 109: 885-94. (Level I).
6. Clark RD. Glucocorticoid receptor antagonists. Curr Top Med Chem., 2008; 8: 813-38. (Level III).
7. Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. Contraception, 2010; 82: 442-52. (Level III).

8. Allen R, O'Brien BM. Uses of misoprostol in obstetrics and gynecology. Rev Obstet Gynecol, 2009; 2: 159-68. (Level III).
9. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol, 1997; 90: 88-92. (Level I).
10. Danielsson KG, Marions L, Rodriguez A, Spur BW, Wong PY, Bygdeman M. Comparison between oral and vaginal administration of misoprostol on uterine contractility. Obstet Gynecol, 1999; 93: 275-80. (Level I).
11. Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod, 2002; 17: 332-6. (Level I).
12. Schaff EA, DiCenzo R, Fielding SL. Comparison of misoprostol plasma concentrations following buccal and sublingual administration. Contraception, 2005; 71: 22-5. (Level II-3).
13. Meckstroth KR, Whitaker AK, Bertisch S, Goldberg AB, Darney PD. Misoprostol administered by epithelial routes: drug absorption and uterine response. Obstet Gynecol, 2006; 108: 582-90. (Level I).
14. Jain JK, Dutton C, Harwood B, Meckstroth KR, Mishell Jr DR. A prospective randomized, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pregnancy. Hum Reprod, 2002; 17: 1477-82. (Level I).
15. Blum J, Raghavan S, Dabash R, Ngoc N, Chelli H, Hajri S, et al. Comparison of misoprostol-only and combined mifepristonemisoprostol regimens for home-based early medical abortion in Tunisia and Vietnam. Int J Gynaecol Obstet, 2012; 118: 166-71. (Level I).
16. Creinin MD. Medical abortion regimens: historical context and overview. Am J Obstet Gynecol, 2000; 183: S3-9. (Level III). [17] Benson J, Clark KA, Gerhardt A, Randall L, Dudley S. Early ab.
17. Benson J, Clark KA, Gerhardt A, Randall L, Dudley S. Early abortion services in the United States: a provider survey. Contraception, 2003; 67: 287-94.
18. Henshaw RC, Naji SA, Russell IT, Templeton AA. Comparison of medical abortion with surgical vacuum aspiration: women's preferences and acceptability of treatment. BMJ, 1993; 307: 714-7.
19. Benson J, Clark KA, Gerhardt A, Randall L, Dudley S. Early abortion services in the United States: a provider survey. Contraception, 2003; 67: 287-94. (Level III).

20. Creinin MD. Randomized comparison of efficacy, acceptability and cost of medical versus surgical abortion. Contraception, 2000; 62: 117-24.
21. Rorbye C, Norgaard M, Nilas L. Medical versus surgical abortion: comparing satisfaction and potential confounders in a partly randomized study. Hum Reprod, 2005; 20: 834-8.
22. Ho PC. Women's perceptions on medical abortion. Contraception, 2006; 74: 11-5.
23. Schaff EA, Stadalius LS, Eisinger SH, Franks P. Vaginal misoprostol administered at home after mifepristone (RU486) for abortion. J Fam Pract, 1997; 44: 353-60.
24. Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. Contraception, 1999; 59: 1-6.
25. MacDonald K, Norman WV, Popescu O. New anomalies due to methotrexate and misoprostol exposure in early pregnancy. Int J Gynaecol Obstet, 2013; 122: 267-8.
26. Creinin MD. Conception rates after abortion with methotrexate and misoprostol. Int J Gynaecol Obstet, 1999; 65: 183-8.
27. Steinhoff PG, Smith RG, Palmore JA, Diamond M, Chung CS. Women who obtain repeat abortions: a study based on record linkage. Fam Plann Perspect, 1979; 11: 30-8.
28. Chen A, Yuan W, Meirik O, Wang X, Wu SZ, Zhou L, et al. Mifepristone-induced early abortion and outcome of subsequent wanted pregnancy. Am J Epidemiol, 2004; 160: 110-7.
29. Oliver-Williams C, Fleming M, Monteath K, Wood AM, Smith GC. Changes in association between previous therapeutic abortion and preterm birth in Scotland, 1980 to 2008: a historical cohort study. PLoS Med., 2013; 10: e1001481.
30. Yarnall J, Swica Y, Winikoff B. Non-physician clinicians can safely provide first trimester medical abortion. Reprod Health Matters, 2009; 17: 61-9.
31. Bednarek PH, Creinin MD, Reeves MF, Cwiak C, Espey E, Jensen JT. Immediate versus delayed IUD insertion after uterine aspiration. Post-Aspiration IUD Randomization (PAIR) Study Trial Group. N Engl J Med., 2011; 364: 2208-17.
32. Saav I, Stephansson O, Gemzell-Danielsson K. Early versus delayed insertion of intrauterine contraception after medical abortion - a randomized controlled trial. PLoS One, 2012; 7.
33. Shimoni N, Davis A, Ramos ME, Rosario L, Westhoff C. Timing of copper intrauterine device insertion after medical abortion: a randomized controlled trial. Obstet Gynecol, 2011; 118: 623-8.

34. Understanding and using the U.S. selected practice recommendations for contraceptive use, 2013. Committee Opinion No. 577. American College of Obstetricians and Gynecologists. Obstet Gynecol, 2013; 122: 1132-3.
35. Mittal S. Contraception after medical abortion. Contraception, 2006; 74: 56-60.
36. U. S. Medical Eligibility Criteria for Contraceptive Use, 2010. Centers for Disease Control and Prevention (CDC). MMWR Recomm Rep., 2010; 59(RR-4): 1-86.
37. Grossman DA, Grindlay K, Buchacker T, Potter JE, Schmertmann CP. Changes in service delivery patterns after introduction of telemedicine provision of medical abortion in Iowa. Am J Public Health, 2013; 103: 73-8.
38. Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. Obstet Gynecol, 2011; 118: 296-303.
39. Warriner IK, Wang D, Huong NT, Thapa K, Tamang A, Shah I, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomised controlled equivalence trial in Nepal. Lancet, 2011; 377: 1155-61.
40. Fonseca W, Alencar AJ, Mota FS, Coelho HL. Misoprostol and congenital malformations. Lancet, 1991; 338: 56.
41. Yip SK, Tse AO, Haines CJ, Chung TK. Misoprostol's effect on uterine arterial blood flow and fetal heart rate in early pregnancy. Obstet Gynecol, 2000; 95: 232-5.
42. Arvidsson C, Hellborg M, Gemzell-Danielsson K. Preference and acceptability of oral versus vaginal administration of misoprostol in medical abortion with mifepristone. Eur J Obstet Gynecol Reprod Biol., 2005; 123: 87-91.
43. Schaff EA, Fielding SL, Westhoff C, Ellertson C, Eisinger SH, Stadalius LS, et al. Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: A randomized trial [published erratum appears in JAMA 2000; 284: 2597]. JAMA, 2000; 284: 1948-53.
44. Blum J, Shochet T, Lynd K, Lichtenberg ES, Fischer D, Arnesen M, et al. Can at-home semi-quantitative pregnancy tests serve as a replacement for clinical follow-up of medical abortion? A US studies. Contraception, 2012; 86: 757-62.
45. Horning EL, Chen BA, Meyn LA, Creinin MD. Comparison of medical abortion follow-up with serum human chorionic gonadotropin testing and in-office assessment. Contraception, 2012; 85: 402-7.

46. Dayananda I, Maurer R, Fortin J, Goldberg AB. Medical abortion follow-up with serum human chorionic gonadotropin compared with ultrasonography: a randomized controlled trial. Obstet Gynecol, 2013; 121: 607-13.
47. Grossman D, Berdichevsky K, Larrea F, Beltran J. Accuracy of a semi-quantitative urine pregnancy test compared to serum betahCG measurement: a possible screening tool for ongoing pregnancy after medication abortion. Contraception, 2007; 76: 101-4.
48. Godfrey EM, Anderson A, Fielding SL, Meyn L, Creinin MD. Clinical utility of urine pregnancy assays to determine medical abortion outcome is limited. Contraception, 2007; 75: 378-82.
49. Cameron ST, Glasier A, Dewart H, Johnstone A, Burnside A. Telephone follow-up and self-performed urine pregnancy testing after early medical abortion: a service evaluation. Contraception, 2012; 86: 67-73.
50. Fiala C, Safar P, Bygdeman M, Gemzell-Danielsson K. Verifying the effectiveness of medical abortion; ultrasound versus hCG testing. Eur J Obstet Gynecol Reprod Biol., 2003; 109: 190-5.
51. Reeves MF, Fox MC, Lohr PA, Creinin MD. Endometrial thickness following medical abortion is not predictive of subsequent surgical intervention. Ultrasound Obstet Gynecol, 2009; 34: 104-9.
52. Grossman D, Grindlay K. Alternatives to ultrasound for follow-up after medication abortion: a systematic review. Contraception, 2011; 83: 504-10.
53. Raymond EG, Weaver MA, Louie KS, Dean G, Porsch L, Lichtenberg ES, et al. Prophylactic compared with therapeutic ibuprofen analgesia in first-trimester medical abortion: a randomized controlled trial. Obstet Gynecol, 2013; 122: 558-64.
54. Raymond EG, Shannon C, Weaver MA, Winikoff B. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception, 2013; 87: 26-37.
55. Reeves MF, Kudva A, Creinin MD. Medical abortion outcomes after a second dose of misoprostol for persistent gestational sac. Contraception, 2008; 78: 332-5.
56. Creinin MD, Vittinghoff E, Keder L, Darney PD, Tiller G. Methotrexate and misoprostol for early abortion: a multicenter trial. I. Safety and efficacy. Contraception, 1996; 53: 321-7.
57. Raymond EG, Weaver MA, Louie KS, Dean G, Porsch L, Lichtenberg ES, et al. Prophylactic compared with therapeutic ibuprofen analgesia in first-trimester medical abortion: a randomized controlled trial. Obstet Gynecol, 2013; 122: 558-64.

58. Creinin MD, Shulman T. Effect of nonsteroidal anti-inflammatory drugs on the action of misoprostolin a regimen for early abortion. Contraception, 1997; 56: 165-8.